

Dyskinesias following neural transplantation in Parkinson's disease

Peter Hagell^{1,4}, Paola Piccini⁶, Anders Björklund², Patrik Brundin³, Stig Rehnström⁵, Håkan Widner^{3,4}, Lesley Crabb⁷, Nicola Pavese⁶, Wolfgang H. Oertel⁹, Niall Quinn⁸, David J. Brooks⁶ and Olle Lindvall^{1,4}

¹Section of Restorative Neurology, ²Division of Neurobiology and ³Section for Neuronal Survival, Wallenberg Neuroscience Center, SE-221 84 Lund, Sweden

⁴Division of Neurology and ⁵Division of Neurosurgery, Department of Clinical Neuroscience, University Hospital, SE-221 85 Lund, Sweden

⁶MRC Clinical Sciences Centre and Division of Neuroscience, Faculty of Medicine, Imperial College, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

⁷National Hospital for Neurology and Neurosurgery and ⁸Sobell Department of Motor Neuroscience and Movement Disorders, Queen Square, London, WC1N 3BG, UK

⁹Department of Neurology, University of Marburg, DE-35033 Marburg, Germany

Correspondence should be addressed to O.L. (olle.lindvall@neuro.lu.se)

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Severe dyskinesias during the 'off' phases (periods of increased Parkinson's disease (PD) disability) have been observed following intrastratial transplantation of human embryonic mesencephalic tissue¹. Here we retrospectively analyzed 14 patients who were followed for up to 11 years after grafting, and found that dyskinesias (abnormal involuntary movements and postures) increased during postoperative off phases, but were generally of mild to moderate severity. Dyskinesia severity was not related to the magnitude of graft-derived dopaminergic re-innervation, as judged by ¹⁸F-labeled 6-L-fluorodopa (FD) positron emission tomography (PET), indicating that off-phase dyskinesias probably did not result from excessive growth of grafted dopaminergic neurons.

All 14 patients showed peak 'on-phase' (periods of little or no PD-related motor disability) dyskinesias before grafting (Table 1). Of 11 cases for which we had access to preoperative video recordings during off phases, six showed some degree of off-phase dyskinesias before transplantation. Mild to moderate foot or neck dystonia (cramp-like abnormal posturing) was observed in three cases, and a fourth had marked foot dystonia. A fifth patient manifested very mild repetitive movements of the right leg and generalized dystonic postures. Finally, one patient showed mild, action-induced choreiform neck movements and hand dystonia.

Hyperkinesias (predominantly choreiform movements) and dystonias increased during off phases after transplantation (Table 2). There were no significant ($P > 0.05$) changes in the severity of peak on-phase dyskinesias (Table 2) or in the percentage of time spent in on-phase with dyskinesias (Table 1). In addition, when the overall degree of dyskinesias in each patient was expressed as a global clinical dyskinesia rating scale (CDRS)² score (Table 2, see footnote), there was a significant ($P = 0.001$) increase during off phases but not during peak on phases. Maximum off-phase global CDRS scores after grafting correlated with peak on-phase scores at the same time point (Spearman's Rho, $r_s = 0.634$, $P = 0.015$; for details of all correlations, see Supplementary Table 1 online), but not with preoperative on- or off-phase scores. Off-phase hyperkinesias and dystonias typically appeared concurrently, either in the same or different body part(s), as choreiform movements intermingled with brief dystonic postures. Repetitive, stereotypic or ballistic movements were also seen. In eight patients, dyskinesias were mild and caused no distress or disability; maximum postoperative off-phase global CDRS scores ranged between 0.5 and 4.5 (median 2.5, interquartile range 1.1–3.8). In the remaining six patients, maximum postoperative off-phase global CDRS scores ranged between 9 and 18 (median 12, interquartile range 10.1–15.4). Only in one case did this constitute a clinical therapeutic problem. Of the six patients with preoperative off-phase dyskinesias, dystonia had increased in three and decreased in three patients at the last postoperative assessment; hyperkinesias had increased in all six patients.

Differential development of off- and on-phase dyskinesias was observed after grafting: two patients with virtually no preoperative off-phase dyskinesias developed mild dyskinesias in off phases after grafting. Concomitantly, their pronounced preoperative on-phase dyskinesias were reduced by >50% postoperatively. Another patient with no preoperative, but pronounced postoperative, off-phase dyskinesias showed virtually no change in peak on-phase dyskinesias. In one of the patients with the most pronounced postoperative off-phase dyskinesias, L-dopa and dopamine agonists were withdrawn for up to nine weeks, with no apparent effect on the dyskinesias.

Table 1. Characteristics of patient group (n = 14) and transplantation procedure.

	At first transplantation	At maximum postoperative off-phase dyskinesias ^a	P-value
Age/duration of PD (years)	52.0 ± 7.0/11.9 ± 2.2	—	—
Hoehn & Yahr stage ^b	3.25 (3–4.25) ^c	—	—
Daily dose of L-dopa equivalents ^d	932.5 ± 477.9	565.4 ± 474.9	0.0004
UPDRS motor score ^{b,e}	42.5 (40.25–55) ^c	27 (19.25–36) ^c	0.002
Time spent in 'off' (%) ^f	36.6 ± 21.1	24.7 ± 20.2	0.095
Time spent in 'on' with dyskinesias (%) ^f	20.6 ± 16.7	14.4 ± 16.6	0.227
VMs implanted in the putamen/caudate nucleus ^g	6.3 ± 2.8/1.1 ± 1.0	—	—

Of 18 patients who were transplanted, four with non-idiopathic PD¹⁰ were excluded. Twelve patients were grafted stereotactically with fresh dissociated VM tissue from 5–9 week-old (postconception) human embryos^{10,11}. In two patients, the tissue was stored at 4°C in a hibernation medium that contained urilazad mesylate and GDNF for 1–8 d before implantation. Data are mean ± s.d. except where indicated. Comparisons were done with paired Student's *t*-tests and—for the UPDRS—Wilcoxon signed-ranks test; $\alpha = 0.05$ (2-tailed). Study procedures were approved by research ethical committees in Lund, London and Munich. ^aRecorded at the time of the highest postoperative off-phase dyskinesia scores for each patient. ^bAs assessed in practically defined 'off' (in the morning ≥12 h after the last dose of anti-parkinsonian medication)¹². ^cMedian (interquartile range). ^dOne-hundred L-dopa equivalents = 100 mg of standard L-dopa = 133 mg of controlled-release L-dopa = 10 mg of bromocriptine = 1 mg of pergolide = 5 mg of ropinirole = 2 mg of apomorphine. ^eOverall parkinsonian symptomatology assessed with the UPDRS motor examination score¹³. ^fMean daily time, as recorded by the patients during the preceding month. ^gPer patient. Grafts were placed unilaterally in the putamen ($n = 2$) and putamen + caudate nucleus ($n = 2$), bilaterally in the putamen + caudate nucleus ($n = 1$), bilaterally in the putamen ($n = 4$) and bilaterally in the putamen + caudate nucleus ($n = 5$).

Table 2. Occurrence of dyskinesias after neural grafting.

	Preoperative ^a	Maximum off-phase dyskinesias ^b	Latest assessment ^c	P-value ^d
Practically defined 'off' phase ^e				
Hyperkinesias	0 (0–0)	4 (0.9–7.5)	3.2 (0.9–7.5)	0.0007
Dystonia	0.5 (0–3)	2.8 (1.4–10.1)	2.8 (0–6.8)	0.042
Peak L-dopa induced 'on' phase ^f				
Hyperkinesias	10 (5.6–13.8)	6 (3.8–11.5)	7 (3.4–14.9)	0.926
Dystonia	5 (1–7.4)	2 (1.9–4.2)	2 (1.8–9.2)	0.924

Dyskinesias were retrospectively scored in random order from videos with the CDRS (maximum score = 28)², by one rater (P.H.) who was blind to the recording dates. Intrarater reliability (intraclass correlation, hyperkinesias = 0.98, dystonia = 0.88) was established *a priori* with separate video sequences². The latest available preoperative video and videos from approximately 12 and 24 months after grafting and (for patients followed beyond that) the latest available postoperative recording were examined. Preoperative videos during off and on periods were unavailable for three and two patients, respectively. Data are median (interquartile range). Unpaired and paired comparisons of CDRS scores, as described in the main text, were done with two-tailed Mann-Whitney U-tests and Wilcoxon signed-ranks tests, respectively ($\alpha = 0.05$). In the main text, overall dyskinesias in each patient are also expressed with a global CDRS score, derived as the sum of the highest hyperkinesia or dystonia ratings from each body part (maximum score, 28; intrarater intraclass coefficient, 0.98). ^aOff, $n = 11$; peak on, $n = 12$. ^bAt a mean of 39.8 months (range 11–132 months) postoperatively; $n = 14$. ^cAt a mean of 44.6 months (range 15–132 months) postoperatively; $n = 14$. ^dA Friedman test was used. ^eAssessed in the morning ≥ 12 h after the last dose of anti-parkinsonian medication¹². ^fPeak 'on' following intake of an individually standardized L-dopa dose, which was the same at each assessment.

The severity of postoperative off-phase dyskinesias tended to correlate negatively with preoperative putaminal FD uptake ($r_s = -0.549$, $P = 0.064$; for scatter-plots, see Supplementary Fig. 1 online). This finding indicates that the manifestation of off-phase dyskinesias after grafting, similar to that of L-dopa-induced on-phase dyskinesias^{3–5}, can be related to the baseline severity of striatal dopaminergic denervation. Our observations argue against the notion that L-dopa-induced on-phase and graft-evoked off-phase dyskinesias have identical underlying mechanisms. The mixed type of dyskinesias seen in off-phases after transplantation is different from that typical of off-phase and on-phase in PD^{6,7}. There was a significant correlation ($r_s = 0.634$; $P = 0.015$) between the severity of peak on and off dyskinesias postoperatively, and the peak on-phase dyskinesia scores were higher in patients with more pronounced off-phase dyskinesias. Thus, in several cases, these adverse effects seemed to be additive after transplantation. However, gradual reduction or no change of peak on-phase dyskinesias after grafting, despite continued development of off-phase dyskinesias, was also seen. This raises the possibility that grafts can not only induce or worsen off-phase dyskinesias but also may ameliorate peak on-phase dyskinesias^{5,8,9}.

Off-phase dyskinesias were not associated with the most marked symptomatic relief. No correlation was found between the improvement of off-phase unified PD rating scale (UPDRS) motor scores and the maximum global postoperative off-phase CDRS scores ($r_s = 0.003$, $P = 0.991$). The degree of motor improvement and reduction in medication did not differ between patients with mild and those with more pronounced postoperative dyskinesias. The evolution of off-phase dyskinesias typically followed a time course that differed from that of symptomatic relief. In the three bilaterally grafted patients who showed the highest postoperative off-phase dyskinesia scores, maximum improvement of UPDRS motor scores occurred by 12 months after transplantation, whereas off-phase dyskinesias reached their maximum at 24–48 months. These data indicate that the mechanisms of graft-derived clinical improvement, believed to be restoration of striatal dopaminergic neurotransmission, most likely differ from those of off-phase dyskinesias.

Our data do not support the idea that off-phase dyskinesias are caused by overgrowth of grafted dopamine neurons. Neither the FD uptake in the scan done closest in time to maximum postop-

erative off-phase dyskinesias ($r_s = -0.132$, $P = 0.652$) nor the increase compared to preoperative values ($r_s = -0.267$, $P = 0.401$) correlated with off-phase global CDRS scores or differed between patients with mild and more pronounced dyskinesias. Nevertheless, such dyskinesias could still be related to dopaminergic mechanisms in the striatum. Small grafts could give rise to dopamine spill-over that reaches supersensitive receptors outside restricted islands of reinnervated striatal areas. Alternatively, off-phase dyskinesias might depend on transplantation-evoked changes in the host striatum or on non-dopaminergic components in the grafts. Thus, global postoperative off-phase CDRS scores correlated with the number of ventral mesencephalon (VM) implanted in the putamen ($r_s = 0.562$, $P = 0.037$). Conspicuously, the two patients who received tissue that had been stored for 1–8 days developed more pronounced off-

phase dyskinesias (global CDRS score: median 15, interquartile range 12–18) than patients implanted with fresh tissue (median 3.5, interquartile range 1.6–10.1). Similarly, the most dramatic post-grafting off-phase dyskinesias reported from other centers were observed after implantation of tissue that had been cultured for up to four weeks¹.

Our findings are contrary to the notion that off-phase dyskinesias are characteristic for dopamine cell replacement *per se* and provide no evidence that this side effect should stop the further development of a cell therapy for PD. However, the underlying mechanisms must be better understood so that off-phase dyskinesias following neural transplantation can be avoided.

Note: Supplementary information is available on the Nature Neuroscience website.

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Competing interests statement

The authors declare that they have no competing financial interests.

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